NEUROCASE
2010, 16 (2), 106–118

Psychology Press
Taylor & Francis Group

# A case of persistent visual hallucinations of faces following LSD abuse: A functional Magnetic Resonance Imaging study

**Giuseppe Iaria,[1,2] Christopher J. Fox,[2] Michael Scheel,[2] Robert M. Stowe,[3] and Jason J. S. Barton[2]**

[1]Department of Psychology, University of Calgary, Calgary, Alberta, Canada
[2]Human Vision and Eye Movement Laboratory, Departments of Medicine (Neurology) and Ophthalmology and Visual Sciences, University of British Columbia, Vancouver, British Columbia, Canada
[3]Departments of Psychiatry and Neurology, University of British Columbia, Vancouver, British Columbia, Canada

In this study, we report the case of a patient experiencing hallucinations of faces that could be reliably precipitated by looking at trees. Using functional Magnetic Resonance Imaging (fMRI), we found that face hallucinations were associated with increased and decreased neural activity in a number of cortical regions. Within the same fusiform face area, however, we found significant decreased and increased neural activity according to whether the patient was experiencing hallucinations or veridical perception of faces, respectively. These findings may indicate key differences in how hallucinatory and veridical perceptions lead to the same phenomenological experience of seeing faces.

***Keywords:*** Faces; Fusiform gyrus; fMRI; LSD abuse; Schizoaffective disorder; Visual hallucinations.

## INTRODUCTION

The neural mechanisms responsible for visual hallucinations are poorly understood. The reason for this paucity of information relies on the fact that visual hallucinations may manifest with a wide range of content and occur in a variety of conditions (Menon, Rahman, Menon, & Dutton, 2003). They may be due to hypnagogic states and visual sensory deprivation in healthy subjects, visual loss in brain damaged patients, neurologic conditions such as epilepsy, diffuse Lewy body disease and peduncular hallucinosis, or psychiatric conditions such as schizophrenia and substance abuse or withdrawal states (Braun, Dumont, Duval, Hamel-Hebert, & Godbout, 2003). In each of these conditions, visual hallucinations may result in seeing simultaneously a variety of objects, people and complex actions performed in familiar or unfamiliar scenes (Oertel et al., 2007), which makes it difficult interpreting the underlying neural mechanisms related to hallucinatory percepts. Here, we had the

We thank Luigi Pizzamiglio and Vince Di Lollo for helpful comments on an early version of the manuscript, and the staff at the UBC MRI Research Centre for technical assistance. This study was supported by operating grants from the National Institute of Mental Health (RO1-MH069898) and Canadian Institutes of Health Research (CIHR) (MOP-77615). GI is supported by the Michael Smith Foundation for Health Research (MSFHR) and the Alzheimer Society of Canada. CJF and MS are supported by the CIHR, and CJF by the MSFHR. JJSB is supported by a Canada Research Chair and a MSFHR Senior Scholar Award.

Address correspondence to Dr Giuseppe Iaria, Department of Psychology, University of Calgary, 2500 University Drive NW – Calgary, Alberta, Canada T2N 1N4. (E-mail: giaria@ucalgary.ca).



http://www.psypress.com/neurocase DOI: 10.1080/13554790903329141

unique opportunity to examine a patient whose visual hallucinations consisted of faces, and which could be produced reliably by staring at trees. The patient's consistent and specific hallucination contents (i.e., faces), together with the selective category of stimuli from which hallucinations can be induced (i.e., trees) provide a rare and ideal condition in which the neural responses related to hallucinatory percepts can be investigated controlling for other factors that may affect the neural activity detected during the complex phenomenon of visual hallucinations. Therefore, we used functional Magnetic Resonance Imaging (fMRI) to investigate the brain activity detected while the patient was experiencing hallucinations, and their effect on specific cortical regions known to be involved in the veridical perception of faces and objects (Barton, 2003; Epstein & Kanwisher, 1998; Haxby, Hoffman, & Gobbini, 2000; Kanwisher, McDermott, & Chun, 1997).

## CASE REPORT

A 49-year-old ambidextrous man reported visual hallucinations of faces when staring at trees. Hallucinations began during a period of weekly lysergic acid diethylamide (LSD) and daily marijuana use at age 21. When they first appeared, he also had messianic and referential delusions, and possible auditory hallucinations, but these have not been present for years. Visual hallucinations have continued despite abstinence from any substances other than tobacco and caffeine for over 10 years. In his early adult years he had also experimented with psilocybin and cocaine. Careful questioning and review of records by two of the authors (RMS and JSSB) revealed no evidence of complex partial epilepsy. The patient had received many psychiatric diagnoses: the most frequent and recent being schizoaffective disorder.

At the time of testing, medications included quetiapine and olanzapine, which have reduced the frequency of hallucinations; carbamazepine and topiramate (prescribed for mood stabilization); and rabeprazole. MRI of the brain was normal. Neuro-ophthalmologic examination showed normal visual acuity, and Goldmann perimetry showed normal peripheral fields. He denies problems recognizing faces and facial expressions.

Although hallucinations have been associated with delusional ideation when he is psychotic, they occur at times when he is nonpsychotic and euthymic, at which time he has preserved insight into their falsity. He experiences the faces as unfamiliar, and having slightly different expressions, but they do not talk, confirming that they represent unimodal visual phenomena. They occur when he is wide awake and he denies narcoleptic symptoms. He also reports that the faces differ between hallucinatory episodes, may appear after a few seconds of staring at a tree, and disappear when gaze shifts. He describes the appearance of these faces as occupying a small part of the bush-tree and randomly located within it. He is not aware of any particular morphology or tree shape that particularly induces the face illusion. They appear more commonly under conditions of bright light, and during the summer months. On occasion, he has sometimes also hallucinated 'stoic faces' when staring at a brick wall.

A detailed neuropsychological assessment (Table 1) revealed general cognitive level within the normal range (TIQ = 95, WASI, Wechsler, 1999), and no attentional, mental imagery, verbal or episodic memory defects. General perceptual abilities were well preserved, as assessed by the Visual Object and Space Perception Battery (Warrington & James, 1991). For face stimuli, while the patient had some difficulty with the Benton Facial Recognition Test (Benton, Sivan, Hamsher, Varney, & Spreen, 1983b) (35/54), his processing of facial expression and identity were normal (Florida Affect Battery; Bowers, Blonder, & Heilman, 1992). After complete description of the study to the patient, written informed consent was obtained.

## fMRI STUDY

To increase the likelihood of including in the fMRI protocol stimuli in which the patient would experience and not experience face hallucinations, we performed a pilot behavioural study consisting of 150 trials, each of which included one colored tree-image displayed in the centre of the scene (without other objects or people). Each trial consisted of a fixation cross presented for 6 s followed by one tree-image presented for unlimited duration: the patient was required to stare at the tree and press a button as soon as the face hallucination started. After the button was pressed the tree-image disappeared and a new trial began. Reaction times were recorded allowing us to determine the duration of steady fixation required

**TABLE 1**
Neuropsychological assessment

| *Cognitive skills and tests* | *Patient's score* | *Performance* |
|---|---|---|
| *Orientation* | | |
| Temporal/Spatial (Wechsler, 1999) | 13/14 | + |
| Left–Right (Benton et al., 1983a) | 20/20 | + |
| *General Intelligence* | | |
| Wechsler Abbreviated Scale of Intelligence (Wechsler, 1999) | | |
| Verbal IQ | 88 | + |
| Performance IQ | 103 | + |
| Full scale IQ | 95 | + |
| Trail Making | | |
| Test A | 34 s | + |
| Test B | 72 s | + |
| *Memory* | | |
| Verbal memory | | |
| Word List (Wechsler, 1997) | | |
| Immediate recall | 26/48 | + |
| Delayed recall (20 min) | 5/12 | + |
| Recognition (20 min) | 23/24 | + |
| Digit span (Wechsler, 1997) | | |
| Forward | 8/16 | + |
| Backward | 5/14 | + |
| Episodic memory (Wechsler, 1997) | | |
| Immediate recall | 31/50 | + |
| Delayed recall (20 min) | 21/50 | + |
| Recognition (20 min) | 22/30 | + |
| Spatial memory | | |
| Corsi Block Test (Wechsler, 1997) | | |
| Forward | 4/16 | * |
| Backward | 5/16 | + |
| Recognition memory (Warrington, 1984) | | |
| Words | 36/50 | * |
| Faces | 38/50 | * |
| *Attention* | | |
| Visual Search (Spinnler & Tognoni, 1987) | 56/60 | + |
| Stars Cancellation Test (Wilson et al., 1987) | 54/54 | + |
| *Visual-perceptual abilities* | | |
| Visual Object and Space Perception Battery (Warrington et al., 1991) | | |
| Object perception | | |
| Screening test | 20/20 | + |
| Incomplete letters | 20/20 | + |
| Silhouettes | 16/30 | + |
| Object decision | 18/20 | + |
| Progressive silhouettes | 8 | + |
| Space perception | | |
| Dot counting | 10/10 | + |
| Position discrimination | 20/20 | + |
| Number location | 8/10 | + |
| Cube analysis | 10/10 | + |
| Judgment of line orientation (Benton et al., 1983b) | 24/30 | + |
| Hooper Visual Organization Test (Hooper, 1983) | 22/30 | + |
| Benton Facial Recognition (Benton et al., 1983c) | 35/54 | * |
| Florida Affect Battery Facial perception (Bowers et al., 1992) | | |
| Identity discrimination | 19/20 | + |
| Affect discrimination | 17/20 | + |
| Name affect | 15/20 | + |
| Select affect | 19/20 | + |
| Match affect | 20/20 | + |
| *Language* | | |
| Boston Naming Test – Short Form (Kaplan et al., 1983) | 15/15 | + |
| *Imagery abilities* | | |
| Mental Rotation Test (Grossi et al., 1991) | 10/10 | + |
| O'clock Test (Grossi et al., 1989) | 46/49 | + |
| Road Map Test (Money et al., 1965) | 26/32 | + |

The table reports the patient's scores included in the neuropsychological evaluation.
*Indicates impaired performances.

for a face hallucination to emerge from each tree-image. We found that the durations before a hallucination appeared ranged from 1.6 to 18.7 s. We selected the 30 tree images that produced hallucinations with less than 3 s of viewing, and the 30 images that only produced hallucinations with more than 7 s of viewing. These two samples of images, which did not differ for contents or physical properties, were then included in the fMRI protocol (each image was presented for 6 s) to increase the likelihood of collecting functional data while the patient was both experiencing and not experiencing face hallucinations.

### Data collection

The patient underwent an MRI scanning session consisting of one anatomical and two fMRI runs, namely the '*tree'* and the '*localizer'* run. During the *tree* run, the patient was presented with the 60 previously selected photographs displaying trees.

Each trial in the '*tree*' run consisted of one image presented for 6 s, followed by a blank screen of the same duration. These 60 trials were randomly intermixed with 30 fixation trials presenting a cross in the centre of the screen (6 s average time). For each trial, the patient was required to press a button as soon as face hallucinations occurred, which allowed us to classify *a posteriori* trials as hallucination and non-hallucination ones.

During the '*localizer'* run the patient viewed photographs of non-living objects (e.g., television, basketball) and faces (neutral and expressive) presented in separate blocks. This typical *functional localizer* allowed us to identify the brain regions involved in the veridical perception of face (Kanwisher et al., 1997) . During the '*localizer'* run, the patient was required to press a button if an image was identical to the previous one (i.e., a standard task adopted to keep subjects focusing on the perceptual processing of the stimuli) (Kanwisher & Yovel, 2006). The '*localizer'* run began and ended with a fixation block showing a cross in the centre of an otherwise blank screen. Additional fixation blocks were alternated with image blocks, with each block lasting 12 s. Six blocks of each image category (object, neutral face, expressive face) intermixed with fixation blocks were randomly presented. Each image block consisted of 15 images (12 novel and 3 repeated), all sized to a width of 400 pixels and presented at screen centre for 500 ms, with an inter-stimulus-interval (ISI) of 300 ms. After this *localizer* run, the patient underwent a 3D structural anatomical scan.

### Data processing and analyses

Images were acquired in a 3.0-Tesla Phillips scanner. Stimuli were presented using Presentation 9.81 software and were rear-projected onto a mirror mounted on the head coil. Whole brain anatomical images were acquired using a T1-weighted echo-planar imaging (EPI) sequence, consisting of 170 axial slices of 1 mm thickness (1 mm gap) with an in-plane resolution of 1×1 mm (FOV = 256). T2-weighted functional runs (TR = 2 s; TE = 30 ms) were acquired using an interleaved ascending EPI sequence, consisting of 36 axial slices of 3 mm thickness (1 mm gap) with an in-plane resolution of 1.875×1.875 mm. The *tree* run consisted of 540 functional volumes, while the *localizer* run consisted of 223 functional volumes. The first volume of each functional run was discarded to allow for scanner equilibration. MRI data were analyzed using BrainVoyager QX Version 1.8 (www.brainvoyager.com). Preprocessing of functional runs consisted of corrections for slice scan time acquisition, head motion (trilinear interpolation), and temporal filtering with a high pass filter in order to remove frequencies less than 3 cycles/time course. The functional runs were co-registered to the patient's anatomical scan, using the first retained functional volume to generate the co-registration matrix. The time course of the *tree* run was analyzed via a single subject GLM, with hallucination (H) and non-hallucination (noH) images (images in which hallucinations occurred or not, respectively) as predictors. Analysis of H>noH was overlaid on the whole brain and significance was set at $p<.05$, with correction for multiple comparisons (Bonferroni). The opposite contrast, noH>H, was performed in order to identify decreased neural activity while experiencing hallucinations.

Similarly to the previous analyses, the *localizer* time course was analyzed with a single subject general linear model (GLM), with object (O) and face (F) (neutral and expressive) as predictors. In order to localize face regions, analysis of F>O was overlaid on the whole brain and significance was set at $p<.05$, with correction for multiple comparisons (False Discovery Rate $q<.05$); the inverse contrast analyses, O>F, was performed to localize object regions. We performed a Region of Interest Analysis (corrected for multiple comparisons and serial

correlations) in which we contrasted the hallucinations and the non-hallucinations trials within both the face and object regions as detected by the *localizer* run.

## Results

During the *tree* run the patient experienced hallucinations in some trials ($n$ = 31) but not in others ($n$ = 29), which allowed us to classify trials as hallucination and non-hallucination ones. Seventeen out of the 31 trials in which the patient experienced hallucinations were stimuli in which during the pilot behavioural study he hallucinated after 7 or more seconds of viewing. However the patient reported also no hallucinations on 14 images that had induced hallucinations within 3 s in the behavioural study. This finding is consistent with the patient's report describing his hallucinations as occurring randomly at different times of exposure and on different stimuli. The almost equal number of trials in which the patient did and did not hallucinate allowed us to analyze his brain activity while performing the task.

The contrast of the fMRI signal across the whole brain during hallucination and non-hallucination trials revealed increased (Figure 1) and decreased (Figure 2) neural activity in both cortical and subcortical regions, including areas involved in early

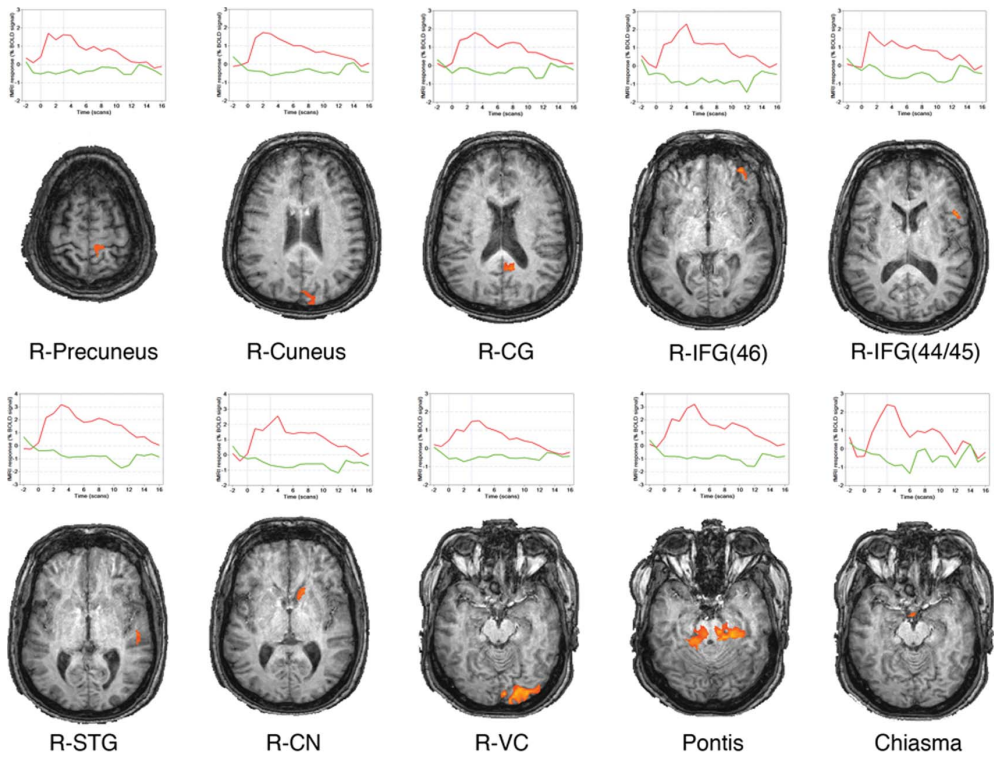


**Figure 1 (above and next page).** Face hallucinations and increased neural activity. Increased neural activity (Talairach coordinates) detected across the whole brain while the patient was experiencing face hallucinations (hallucination minus non-hallucination trials). For each brain activity, the diagram shows the BOLD responses according to the hallucination (red) and non-hallucination (green) trials. R, right hemisphere; L, left hemisphere. R-Precuneus ($X$ = 9, $Y$ = –52, $Z$ = 58; peak $t$ value = 6.76); R-Cuneus ($X$ = 9, $Y$ = –94, $Z$ = 25; peak $t$ value = 5.83); R-CG, Cingulate Gyrus ($X$ = 9, $Y$ = –55, $Z$ = 19; peak $t$ value = 6.18); R-IFG(46), Inferior Frontal Gyrus (Brodmann Area 46) ($X$ = 36, $Y$ = 41, $Z$ = 13; peak $t$ value = 6.91); R-IFG(44/45), Inferior Frontal Gyrus (Brodmann Areas 44 and 45) ($X$ = 51, $Y$ = 14, $Z$ = 10; peak $t$ value = 6.95); R-STG, Superior Temporal Gyrus ($X$ = 54, $Y$ = –31, $Z$ = 4; peak $t$ value = 6.28); R-CN, Caudate Nucleus ($X$ = 18, $Y$ = 17, $Z$ = 4; peak $t$ value = 6.35); R-VC, Visual Cortex ($X$ = 18, $Y$ = –91, $Z$ = –5; peak $t$ value = 7.37); Chiasma ($X$ = 0, $Y$ = –1, $Z$ = –14; peak $t$ value = 6.49); L-SFG, Superior Frontal Gyrus ($X$ = –30, $Y$ = –13, $Z$ = 55; peak $t$ value = 6.96); L-Precuneus ($X$ = –6, $Y$ = –58, $Z$ = 52; peak $t$ value = 6.99); L-MFG, Middle Frontal Gyrus ($X$ = –30, $Y$ = –1, $Z$ = 49; peak $t$ value = 6.8); L-Precentral, Precentral Gyrus ($X$ = –51, $Y$ = –10, $Z$ = 31; peak $t$ value = 6.45); L-Insula ($X$ = –36, $Y$ = –4, $Z$ = 19; peak $t$ value = 6.32); L-STG, Superior Temporal Gyrus ($X$ = –54, $Y$ = –49, $Z$ = 19; peak $t$ value = 7.0); L-CN, Caudate Nucleus ($X$ = –15, $Y$ = 17, $Z$ = 7; peak $t$ value = 6.61); L-LG, Lingual Gyrus ($X$ = –3, $Y$ = –61, $Z$ = 1; peak $t$ value = 6.09); L-VC, Visual Cortex ($X$ = 9, $Y$ = –82, $Z$ = –5; peak $t$ value = 7.47); L-FG, Fusiform Gyrus ($X$ = –45, $Y$ = –31, $Z$ = –11; peak $t$ value = 6.51). To view this figure in color, please visit the online version of this Journal.

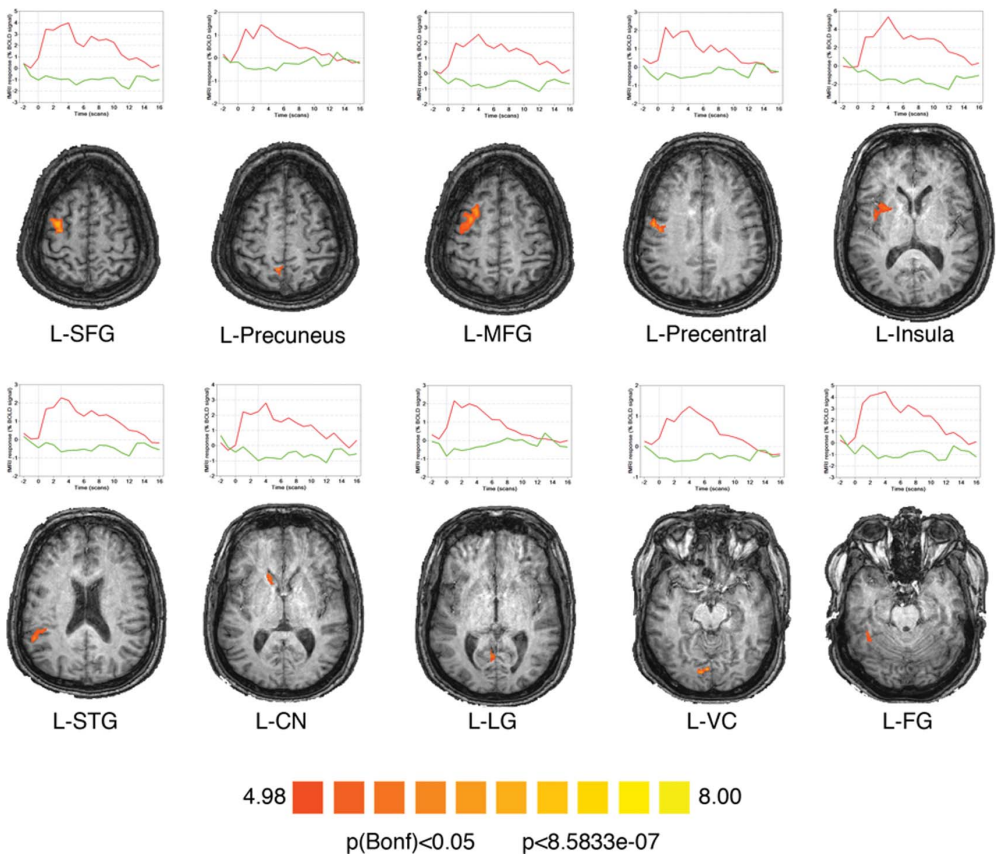


**Figure 1.** (*Continued*).

visual processing (Brodmann's areas 17, 18, 19). As shown in details in Figures 1 and 2, in each of these regions, difference in brain activity between hallucination and non-hallucination images was due to increased and decreased neural responses while the patient experienced visual hallucinations.

During the *localizer* run, the contrast between faces and non-living objects allowed us to identify the patient's right fusiform face area (FFA) in the occipitotemporal cortex, as well as regions in the superior and middle frontal gyrus bilaterally (Table 2); whereas the opposite contrast (objects minus faces) was able to localize regions more responsive to objects such as the lateral occipital complex (LOC) and the parahippocampal place area (PPA) (Epstein & Kanwisher, 1998) bilaterally (Table 2).

The contrast between images of trees in which the patient was and was not hallucinating revealed a statistically significant increase in neural activity during hallucination trials in the frontal regions bilaterally within the face regions, and in the left PPA within the object regions (Table 2). Within the FFA, the difference in BOLD signal change between hallucinations and non-hallucinations trials revealed a trend showing a decreased neural response while hallucinating compared to non-hallucination trials, but this difference did not reach statistical significance ($p = .18$). Importantly, however, the decreased neural activity in the fusiform gyrus detected in the whole brain analysis while the patient was experiencing face hallucinations fully overlapped with the FFA identified in the *localizer run* while the patient was processing veridical percepts of faces (Figure 3), confirming that BOLD signal change in this functionally selective region increases during veridical perception of face and significantly decreases while the patient experiences face hallucinations.

## Controlling for the fMRI stimuli

The sample of images included in this fMRI study consisted of trees that did not differ in specific local or configural features. A qualitative inspection of

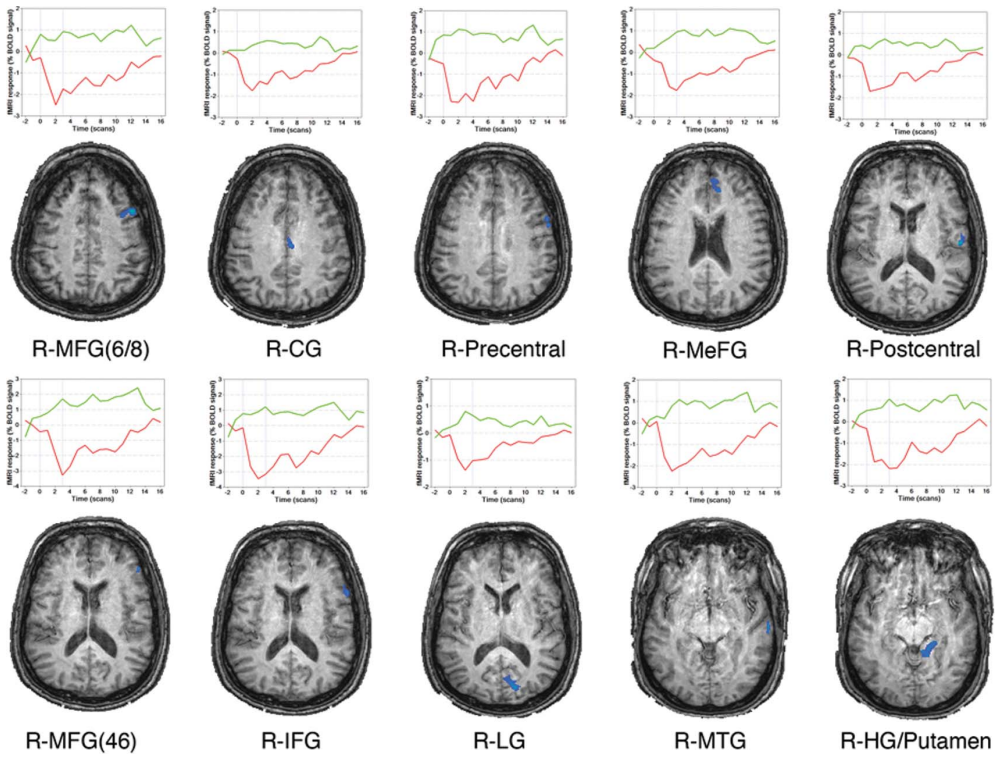


**Figure 2 (above and next page).** Face hallucinations and decreased neural activity. Decreased neural activity (Talairach coordinates) detected across the whole brain while the patient was experiencing face hallucinations (non-hallucination minus hallucination trials). For each brain activity, the diagram shows the BOLD responses according to the hallucination (red) and non-hallucination (green) trials. R, right hemisphere; L, left hemisphere. R-MFG(6/8), Middle Frontal Gyrus (Brodmann Areas 6 and 8) ($X = 45$, $Y = 11$, $Z = 40$; peak $t$ value = 6.94); R-CG, Cingulate Gyrus ($X = 3$, $Y = -13$, $Z = 36$; peak $t$ value = 6.42); R-Precentral, Precentral Gyrus ($X = 57$, $Y = -4$, $Z = -31$; peak $t$ value = 6.83); R-MeFG, Medial Frontal Gyrus ($X = 8$, $Y = 42$, $Z = 23$; peak $t$ value = 6.84); R-Postcentral, Postcentral Gyrus ($X = 54$, $Y = -16$, $Z = 16$; peak $t$ value = 7.32); R-MFG(46), Middle Frontal Gyrus (Brodmann Area 46) ($X = 51$, $Y = 35$, $Z = 13$; peak $t$ value = 6.35); R-IFG, Inferior Frontal Gyrus ($X = 66$, $Y = 11$, $Z = 10$; peak $t$ value = 6.81); R-LG, Lingual Gyrus ($X = 13$, $Y = -75$, $Z = 10$; peak $t$ value = 6.6); R-MTG, Middle Temporal Gyrus ($X = 60$, $Y = -22$, $Z = -5$; peak $t$ value = 6.96); R-HG/Putamen, Hippocampal Gyrus and Putamen ($X = 14$, $Y = -38$, $Z = -7$; peak $t$ value = 6.58); R-FG, Fusiform Gyrus ($X = 40$, $Y = -40$, $Z = -20$; peak $t$ value = 6.1); L-SFG, Superior Frontal Gyrus ($X = -12$, $Y = 3$, $Z = 62$; peak $t$ value = 6.62); L-MeFG, Medial Frontal Gyrus ($X = -15$, $Y = 47$, $Z = 31$; peak $t$ value = 6.26); L-IFG, Inferior Frontal Gyrus ($X = -50$, $Y = 17$, $Z = 15$; peak $t$ value = 6.98); L-MFG, Middle Frontal Gyrus ($X = -32$, $Y = 56$, $Z = 12$; peak $t$ value = 6.51); L-LG, Lingual Gyrus ($X = -5$, $Y = -59$, $Z = 10$; peak $t$ value = 6.74); L-Putamen ($X = -14$, $Y = -29$, $Z = 0$; peak $t$ value = 7.15); L-MTG, Middle Temporal Gyrus ($X = -51$, $Y = -21$, $Z = -6$; peak $t$ value = 6.92); L-FG, Fusiform Gyrus ($X = -35$, $Y = -45$, $Z = -15$; peak $t$ value = 5.98); L-STG, Superior Temporal Gyrus ($X = -40$, $Y = 13$, $Z = -34$; peak $t$ value = 6.68). To view this figure in color, please visit the online version of this Journal.

the two samples of images in which the patient was experiencing or not hallucinations did not result in any selective characteristic of the images that was able to discriminate among samples, as also assessed by two healthy individuals (blind to the identity of the hallucination and non-hallucinations trials) who categorized the images using tree-features criteria. In addition, the fact that hallucinations were triggered by different stimuli (and at different times) between the behavioural pilot study and the fMRI experiment support the conclusion that their occurrence is not consistently related to specific properties of these stimuli. However, to exclude the possibility that differences in BOLD signal between hallucination and non-hallucination trials might be due to differences in the tree images that neither healthy individuals nor the patient were able to detect explicitly, we performed the same fMRI experiment in a healthy 48-year-old ambidextrous control subject with no neurological or psychiatric history, no prior episodes of hallucinations, and no difficulty with face recognition. fMRI protocol (*localizer* and *tree* runs) data acquisition and analyses were identical to the ones performed in the patient's study. During the *tree* run we showed to the control subject the same tree

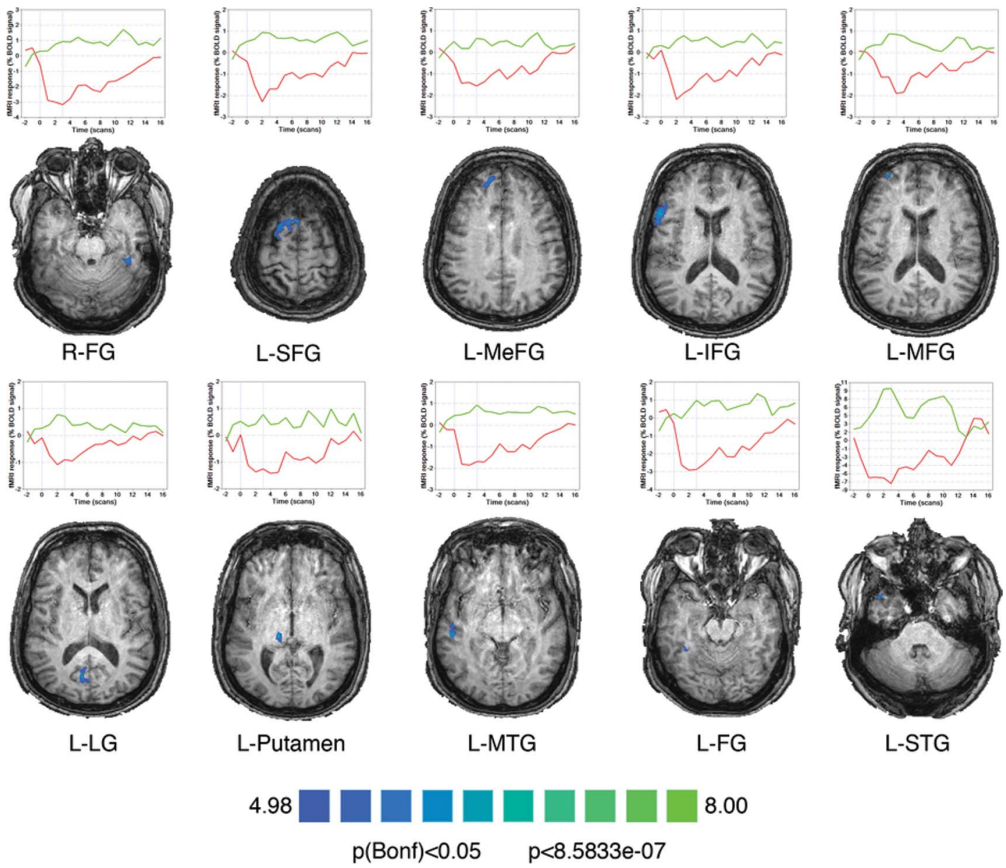


**Figure 2.** (*Continued*).

images that we presented to the patient, and asked him to stare at the images. Whole brain analyses did not reveal any significant difference when contrasting the images corresponding to the patient's hallucinatory and non-hallucinatory trials. Likewise, after successfully localizing the control's face and objects areas (*localizer* run), the ROI analysis on these regions failed to reveal any significant difference in BOLD signal change between the hallucinatory and non-hallucinatory trials (Table 2).

## DISCUSSION

Complex visual hallucinations can be caused by many different disorders (Manford & Andermann, 1998). Among subjects with normal mental status, these include release hallucinations with visual loss, seizures, and migraine. In our patient, there was no evidence of visual loss, there were no convincing clinical or electrophysiological findings to suggest focal epilepsy, and the hallucinations he experiences only occur in a few specific visual contexts, and are distinctly different from migraine auras. Hallucinations can also occur with intoxication, delirium and dementia, none of which apply to this patient. Rather, his hallucinations clearly date back to a period of heavy LSD abuse, and are consistent with reports of persistent visual phenomena after such abuse, a syndrome recognized in the Diagnostic and Statistical Manual of the American Psychiatric Association as 'Hallucinogen Persisting Perceptual Disorder' (HPPD). A comprehensive review of the many publications on this topic found the literature to lack methodological rigor (Halpern & Pope, 2003), and few papers discuss possible underlying biological mechanisms, which might include kindling, long-term potentiation or depression in specific areas, and changes in the expression of genes involved in synaptic plasticity in prefrontal cortical neurons (Nichols & Sanders-Bush, 2004). However, it is not clear that the various visual phenomena described by the very small minority of hallucinogen users reported

**TABLE 2**
Face and object regions as detected by the functional localizer

| *Anatomical region (Brodmann area)* | *Talairach coordinates* | | | *Peak t value* | *Hall (SE)* | *Non-hall (SE)* | *t-Test* |
|---|---|---|---|---|---|---|---|
| | *X* | *Y* | *Z* | | | | |
| **Patient** | | | | | | | |
| *Face regions (faces minus objects)* | | | | | | | |
| Right FFA | 36 | –40 | –23 | 5.17 | –0.866 (.68) | 0.356 (.68) | $t = –1.35$; $p = .18$ |
| Right superior frontal gyrus (9) | 9 | 44 | 40 | 4.16 | –0.443 (.38) | –0.259 (.38) | $t = –0.40$; $p = .7$ |
| Right middle frontal gyrus (10) | 33 | 53 | –2 | 4.74 | 1.528 (.49) | –0.118 (.49) | $t = 2.56$; $p = .011$* |
| Left superior frontal gyrus (9) | –15 | 44 | 13 | 5.05 | 0.572 (.31) | –0.223 (.31) | $t = 1.98$; $p = .048$* |
| Left middle frontal gyrus (9/46) | –39 | 26 | 31 | 4.59 | –0.682 (.54) | 0.135 (.54) | $t = –1.22$; $p = .2$ |
| *Object regions (objects minus faces)* | | | | | | | |
| Right PPA | 27 | –52 | –11 | 7.64 | 0.653 (.24) | 0.477 (.24) | $t = 0.63$; $p = .5$ |
| Right LOC | 51 | –64 | –8 | 4.19 | 0.35 (.19) | 0.25 (.19) | $t = 0.45$; $p = .6$ |
| Left PPA | –24 | –49 | –14 | 5.61 | 1.654 (.34) | 0.263 (.34) | $t = 3.19$; $p = .0015$* |
| Left LOC | –42 | –69 | –13 | 4.13 | 0.39 (.23) | 0.15 (.23) | $t = 0.869$; $p = .4$ |
| **Control subject** | | | | | | | |
| *Face regions (faces minus objects)* | | | | | | | |
| Right FFA | 33 | –49 | –17 | 9.93 | 0.179 (.14) | 0.112 (.11) | $t = 0.48$; $p = .6$ |
| Left FFA | –36 | –49 | –20 | 5.35 | 0.894 (.15) | 0.82 (.15) | $t = –0.42$; $p = .7$ |
| Right STS (21/22) | 57 | –49 | 7 | 4.28 | –0.735 (.21) | –0.82 (.21) | $t = 0.31$; $p = .8$ |
| Left STS (21/22) | –48 | –46 | 7 | 6.85 | 0.068 (.55) | 0.098 (.55) | $t = –0.13$; $p = .9$ |
| Right superior frontal gyrus (10) | 18 | 62 | 22 | 6.13 | –0.101 (.10) | –0.145 (.10) | $t = 0.34$; $p = .7$ |
| Right inferior frontal gyrus (46) | 42 | 41 | 13 | 4.49 | –0.033 (.11) | –0.032 (.11) | $t = –0.003$; $p = 1$ |
| Left middle frontal gyrus (9/46) | –51 | 29 | 22 | 4.98 | 0.287 (.20) | 0.118 (.20) | $t = 0.7$; $p = .5$ |
| Right inferior parietal lobe (40) | 42 | –40 | 37 | 5.23 | –0.05 (10) | –0.111 (.10) | $t = 0.47$; $p = .6$ |
| *Object regions (objects minus faces)* | | | | | | | |
| Right PPA | 21 | –34 | –17 | 7.56 | 1.053 (.15) | 0.936 (.15) | $t = 0.64$; $p = .5$ |
| Right LOC | 36 | –73 | –5 | 9.36 | 1.251 (.10) | 1.191 (.10) | $t = 0.48$; $p = .6$ |
| Left LOC | –39 | –73 | –11 | 6.96 | 1.054 (.12) | 0.987 (.12) | $t = 0.47$; $p = .6$ |

The table reports the Talairach coordinates and peak activity of each identified region in both the patient and the control subject, as well as the BOLD signal change detected in each region during the hallucination (Hall) and non-hallucination (Non-hall) images, and the result of the *t*-test comparing the two BOLD signal changes.
*Indicates statistical significant effect ($p<.05$). SE refers to standard errors. FFA, Fusiform Face Area; PPA, Parahippocampal Place Area; LOC, Lateral Occipital Complex.

to be afflicted with HPPD represent a biological consequence of hallucinogen abuse as opposed to increased vulnerability to dissociative phenomena in susceptible individuals. Individuals suffering from schizophrenia have an increased tendency to 'physiognomize' their visual environment, i.e., to perceive illusory patterns and shapes, including faces, emerging out of various visual backgrounds, including trees and bushes, clouds, and flames, a phenomenon that is also commonplace during acute hallucinogen intoxication (Harrington, Oepen, & Spitzer, 1989). Whether mood instability plays a modulatory role can be questioned; however, it is clear that the hallucinations themselves frequently occur when he is nonpsychotic, which also rules out a carbamazepine or topiramate-related anticonvulsant-induced psychosis.

While our data agree with the majority of studies showing increased BOLD signal changes in many visual and non-visual areas during hallucinatory periods (Allen, Laroi, McGuire, & Aleman, 2008; Ffytche et al., 1998; Silbersweig et al., 1995) (Figure 1), they provide the new observation that during hallucinations *decreased* neural activity occurs in similar regions located all over the brain (Figure 2). In addition, within selective brain regions responding more to faces or objects, during hallucinations we detected an increased neural response in frontal areas bilaterally and in the left parahippocampal cortex (PPA) (Table 2). These increased neural activities may reflect additional attentional demands while processing the stimuli and monitoring the hallucinations, which may occur in both face frontal regions as well as in

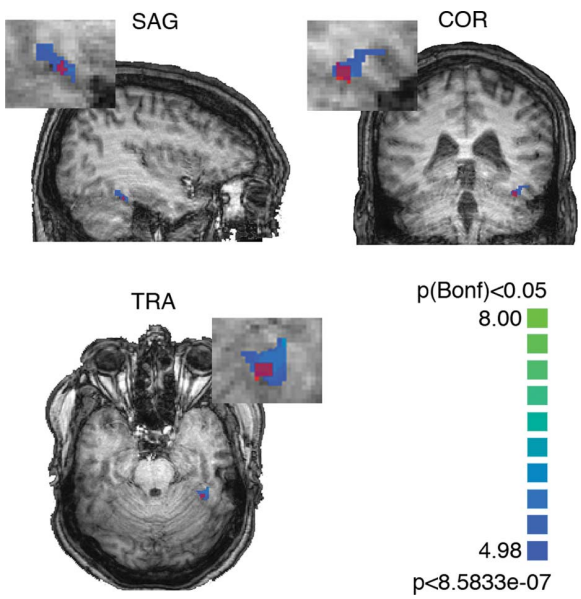


**Figure 3.** Neural activity in the fusiform face area. Sagittal, Coronal and Transversal views (and zoomed views) of the increased neural activity detected within the FFA during veridical perception of face (red; $X = 40$, $Y = -40$, $Z = -20$; peak $t$ value = −6.1) overlapping with the decreased BOLD signal change detected during face hallucinations (blue; $X = 36$, $Y = -40$, $Z = -23$; peak $t$ value = 5.17). To view this figure in color, please visit the online version of this Journal.

regions in which objects are processed preferentially (PPA). On the other hand, significant decreased neural activity was detected in the right fusiform gyrus, a region that clearly overlapped with the fusiform face area as identified by the functional *localizer run* (Figure 3).

Within the same region, the increased neural response during veridical percept of faces is in sharp distinction with its decreased signal detected while the patient experienced hallucinations, suggesting that hallucinations may be generated by mechanisms that significantly differ from those operating during veridical perception (Allen et al., 2007; De Haan, Nys, van Zandvoort, & Ramsey, 2007; Holroyd & Wooten, 2006).

This finding is not consistent with a prior report suggesting that hallucinations might be associated with increased signal in regions specialized for the content of the hallucination. Ffytche et al. (1998) studied four patients with visual hallucinations from Charles Bonnet syndrome due to ocular causes of visual loss and found that hallucinations of colour, objects and faces were associated with patterns of increased neural activity that corresponded approximately to known cortical centres for colour, object and face processing. However, this study did not (or possibly could not, given the visual loss) use functional localizers to confirm the location of these cortical centres. Moreover, the content of their patients' hallucinations was variable. The one subject who hallucinated faces also saw bright greenish white light and shadows, with activity posterior to the usual location of the fusiform face area, as the authors acknowledged. In addition, the result reported for this patient with face hallucinations is surprising in that increased activity was found in the left rather than the right fusiform gyrus, contrary to the usual predominance of right-sided activation when healthy subjects view faces (Kanwisher & Yovel, 2006).

How can we interpret decreased fMRI BOLD signal during hallucinatory percepts in cortical areas defined by increased signal during veridical perception? BOLD signal change may reflect a number of different cortical events, including local field potentials related to interneuron activity, neuronal spiking, and significantly, either inhibitory or excitatory synaptic inputs (Lauritzen, 2005; Logothetis, Pauls, Augath, Trinath, & Oeltermann, 2001; Mukamel et al., 2005). The suggestion that inhibitory input can be correlated with BOLD signal change is supported by observations in different regions (Stefanovic, Warnking, & Pike, 2004), such as the increase in BOLD signal in the frontal eye field during antisaccades (Manoach et al., 2007), which single cell recordings show to be associated with reduced neural activity (and likely increased inhibitory inputs) in this region (Everling & Munoz, 2000). Thus, disinhibition of visual cortex during hallucinations could be reflected in less inhibitory synaptic input and therefore less BOLD signal while they were occurring. This would contrast with the normal increase in BOLD signal in the critical area during veridical perception, in which visual activity is generated by increased excitatory input to that critical area. This, however, remains a speculation and further studies are needed to verify this hypothesis. Alternatively, considering more conventional assumptions that decreased BOLD activity is a marker of inactivation in the affected area, it could be hypothesized that frontal *hyper*activity and fusiform gyrus *hypo*activity during hallucinations in our patient reflected *active, frontally-mediated inhibition* of 'bottom up' processing in posterior areas, favouring internally generated representations over veridical 'percepts'

generated in peristriate areas. This hypothesis could explain the trial-to-trial variability in the induction of hallucinations during the experiment with the same stimuli. Auto-suggestion is hypothesized to underlie conversion disorder symptoms and signs in highly hypnotizable individuals with somatoform disorder, and a recent fMRI experiment in three subjects with unexplained unilateral numbness diagnosed with conversion disorder showed a failure to activate the contralateral S1 during unilateral stimulation of the affected limb, but bilateral activation of S1 with double simultaneous stimulation (Ghaffar, Staines, & Feinstein, 2006). This result, as well as those of similar studies in sensorimotor conversion disorder, is best explained by the hypothesis that active inhibition of the cortical areas primarily responsible for the 'impaired' function in question is involved, with bilateral stimulation serving as a distraction that makes it difficult to maintain this inhibition (Hurwitz, & Prichard, 2006). Kosslyn, Thompson, Costantini-Ferrando, Alpert, and Spiegel (2000) found that hypnotic suggestion of colour-scale perception of a gray-scale pattern induced bilateral *hyper*metabolism in fusiform and/or lingual gyri regions involved in colour perception, whereas the reverse suggestion (to perceive a coloured pattern in gray scale) was associated with bilateral *hypo*metabolism in the same areas, again consistent with a hypothesis that active inhibition of sensory areas may be involved in altered perceptual processing invoked by suggestibility (whether internally or externally driven). Finally, it is intriguing that increased metabolism of prefrontal cortical regions during acute intoxication with psilocybin and mescaline (hallucinogens whose psychotomimetic effects are felt to share with LSD a common mechanism that involves 5-HT2A receptor activation), has been demonstrated with FDG-PET (Vollenweider et al., 1997) and SPECT (Hermle, Gouzoulis-Mayfrank, & Spitzer, 1998), respectively.

The hallucinations described by our patient may represent an instance of pareidolia, i.e., the phenomenon of seeing images from shapes (Sims, 2002). Indeed, one of the most common phenomenological symptoms of pareidolic illusions is the perception of faces in structures with low information content (Summerfield, Egner, Mangels, & Hirsch, 2006). Such a phenomenon has been reported in a variety of clinical populations including patients with LSD flashbacks (Abraham, 1983) and methamphetamine intoxication (Nakatani & Hara, 1998). More recently, a similar case of pareidolia has been described in a patient diagnosed with obsessive–compulsive disorder (OCD) who reported visualizing faces out of floor tiles (with symptoms responding to treatment with serotonin reuptake inhibitors) (Fontenelle, 2008). Although the hallucinatory perception experienced by our patient seems to be similar to the ones described in other cases, his hallucinations reportedly occur more frequently under conditions of high luminance, whereas the opposite would ordinarily be expected with pareidolia.

In a recent study, Hadjikhani, Kveraga, Naik, and Ahlfors (2009), replicated the phenomenon of pareidolia in healthy subjects by using objects that were incidentally perceived as faces (i.e., face-like objects). The authors used magnetoencephalography (MEG) to investigate the activity of brain regions involved in face processing while participants were perceiving real faces and face-like objects. The results showed that both faces and face-like objects were able to evoke the same early (165 ms) activation within the ventral fusiform cortex, a region well-known to be involved in the processing of faces. No activation was found in the same area when participants were presented with common objects. The authors suggest that the perception of face-like objects, as well as the perception of real faces, occur at an early processing stage. Although our study differs in many aspects from the one described above, there was evidence in both of increased signal during veridical perception of faces, while in our study, *decreased* BOLD signal was observed in the same area when the subject was experiencing hallucinatory perception of faces. This may suggest that the phenomenon of pareidolia and the phenomenon of visual hallucination may be subserved by different neural mechanisms, although they may present with a similar phenomenological experience.

In summary, in this study we provide evidence for both increased and decreased brain activity occurring during hallucinations, suggesting key difference in the neural mechanisms between visual hallucinations and veridical perception. These findings, however, need to be treated with caution since they refer to a single case study in a patient with a history of schizoaffective disorder and 'hallucinogen persisting perceptual disorder'. Nevertheless, we believe that our study may be relevant for further research aiming at shedding more light on the genesis of a complex phenomenon such as visual hallucinations.

Original manuscript received 25 January 2009
Revised manuscript accepted 8 September 2009
First published online 18 November 2009

## REFERENCES

Abraham, H. D. (1983). Visual phenomenology of the LSD flashback. *General Archives of Psychiatry*, *40*(8), 884–889.

Allen, P., Amaro, E., Fu, C. H., Williams, S. C., Brammer, M. J., Johns, L. C., et al. (2007). Neural correlates of the misattribution of speech in schizophrenia. *British Journal of Psychiatry*, *190*, 162–169.

Allen, P., Laroi, F., McGuire, P. K., & Aleman, A. (2008). The hallucinating brain: A review of structural and functional neuroimaging studies of hallucinations. *Neuroscience & Biobehavioral Reviews*, *32*(1), 175–191.

Barton, J. J. (2003). Disorders of face perception and recognition. *Neurology Clinic*, *21*(2), 521–548.

Benton, A. L., Sivan, A. B., Hamsher, K. d. S., Varney, N. R., & Spreen, O. (1983a). *Contribution to neuropsychological assessment*. New York: Oxford University Press.

Benton, A. L., Sivan, A. B., Hamsher, K. d. S., Varney, N. R., & Spreen, O. (1983b) *Facial recognition: Stimulus and multiple choice pictures; contributions to neuropsychological assessment*. New York: Oxford University Press.

Bowers, D., Blonder, L., & Heilman, K. M. (1992). *The Florida Affect Battery*. Gainesville, FL: Center for Neuropsychological Studies, University of Florida.

Braun, C. M., Dumont, M., Duval, J., Hamel-Hebert, I., & Godbout, L. (2003). Brain modules of hallucination: an analysis of multiple patients with brain lesions. *Journal of Psychiatry & Neuroscience*, *28*(6), 432–449.

De Haan, E. H., Nys, G. M., van Zandvoort, M. J., & Ramsey, N. F. (2007). The physiological basis of visual hallucinations after damage to the primary visual cortex. *Neuroreport*, *18*(11), 1177–1180.

Epstein, R., & Kanwisher, N. (1998). A cortical representation of the local visual environment. *Nature*, *392*(6676), 598–601.

Everling, S., & Munoz, D. P. (2000). Neuronal correlates for preparatory set associated with pro-saccades and anti-saccades in the primate frontal eye field. *Journal of Neuroscience*, *20*(1), 387–400.

Ffytche, D. H., Howard, R. J., Brammer, M. J., David, A., Woodruff, P., & Williams, S. (1998). The anatomy of conscious vision: An fMRI study of visual hallucinations. *Nature Neuroscience*, *1*(8), 738–742.

Fontenelle, L. F. (2008). Pareidolias in obsessive–compulsive disorder: Neglected symptoms that may respond to serotonin reuptake inhibitors. *Neurocase*, 14(5), 414–418.

Ghaffar, O., Staines, W. R., & Feinstein, A. (2006). Unexplained neurologic symptoms: An fMRI study of sensory conversion disorder. *Neurology*, *67*(11), 2036–2038.

Grossi, D. (1991) *La riabilitazione dei disordini della cognizione spaziale*. Milano: Masson.

Grossi, D., Modafferi, A., Pelosi, L., & Trojano, L. (1989). On the different roles of the cerebral hemispheres in mental imagery: The 'o'clock test' in two clinical cases. *Brain and Cognition*, *10*, 18–27.

Hadjikhani, N., Kveraga, K., Naik, P., & Ahlfors, S. P. (2009). Early (M170) activation of face-specific cortex by face-like objects. *Neuroreport*, *20*(4), 403–407.

Halpern, J. H., & Pope Jr, H. G. (2003). Hallucinogen persisting perception disorder: What do we know after 50 years? *Drug and Alcohol Dependence*, *69*(2), 109–119.

Harrington, A., Oepen, G., & Spitzer, M. (1989). Disordered recognition and perception of human faces in acute schizophrenia and experimental psychosis. *Comprehensive Psychiatry*, *30*(5), 376–384.

Haxby, J. V., Hoffman, E. A., & Gobbini, M. I. (2000). The distributed human neural system for face perception. *Trends in Cognitive Sciences*, *4*(6), 223–233.

Hermle, L., Gouzoulis-Mayfrank, E., & Spitzer, M. (1998). Blood flow and cerebral laterality in the mescaline model of psychosis. *Pharmacopsychiatry*, *31*(S2), 85–91.

Holroyd, S., & Wooten, G. F. (2006). Preliminary FMRI evidence of visual system dysfunction in Parkinson's disease patients with visual hallucinations. *Journal of Neuropsychiatry and Clinical Neurosciences*, *18*(3), 402–404.

Hooper, H. E. (1983). *The Hooper visual organisation test manual*. Los Angeles, CA: Western Psychological Services.

Hurwitz, T. A., & Prichard, J. W. (2006). Conversion disorder and fMRI. *Neurology*, *67*(11), 1914–1915.

Kanwisher, N., & Yovel, G. (2006). The fusiform face area: A cortical region specialized for the perception of faces. *Philosophical Transactions of the Royal Society of London B: Biologcal Sciences*, *361*(1476), 2109–2128.

Kanwisher, N., McDermott, J., & Chun, M. M. (1997). The fusiform face area: A module in human extrastriate cortex specialized for face perception. *Journal of Neuroscience*, *17*(11), 4302–4311.

Kaplan, E., Goodglass, H., & Weintraub, S. (1983). *The Boston Naming Test*. Philadelphia, PA: Lea & Febiger.

Kosslyn, S. M., Thompson, W. L., Costantini-Ferrando, M. F., Alpert, N. M., & Spiegel, D. (2000). Hypnotic visual illusion alters color processing in the brain. *American Journal of Psychiatry*, *157*(8), 1279–1284.

Lauritzen, M. (2005). Reading vascular changes in brain imaging: Is dendritic calcium the key? *Nature Reviews Neuroscience*, *6*(1), 77–85.

Logothetis, N. K., Pauls, J., Augath, M., Trinath, T., & Oeltermann, A. (2001). Neurophysiological investigation of the basis of the fMRI signal. *Nature*, *412*(6843), 150–157.

Manford, M., & Andermann, F. (1998). Complex visual hallucinations: Clinical and neurobiological insights. *Brain*, *121*, 1819–1840.

Manoach, D. S., Thakkar, K. N., Cain, M. S., Polli, F. E., Edelman, J. A., Fischl, B., et al. (2007). Neural

activity is modulated by trial history: A functional magnetic resonance imaging study of the effects of a previous antisaccade. *Journal of Neuroscience*, *27*(7), 1791–1798.

Menon, G. J., Rahman, I., Menon, S. J., & Dutton, G. N. (2003). Complex visual hallucinations in the visually impaired: The Charles Bonnet Syndrome. *Survey of Ophthalmology*, *48*(1), 58–72.

Money, J., Alexander, D., & Walker, H. T. (1965) *A standardized road map test of direction sense*. Baltimore, MD: The Johns Hopkins Press.

Mukamel, R., Gelbard, H., Arieli, A., Hasson, U., Fried, I., & Malach, R. (2005). Coupling between neuronal firing, field potentials, and FMRI in human auditory cortex. *Science*, *309*(5736), 951–954.

Nakatani, Y., & Hara, T. (1998). Disturbance of consciousness due to methamphetamine abuse: A study of 2 patients. *Psychopathology*, *31*(3), 131–137.

Nichols, C. D., & Sanders-Bush, E. (2004). Molecular genetic responses to lysergic acid diethylamide include transcriptional activation of MAP kinase phosphatase-1, C/EBP-beta and ILAD-1, a novel gene with homology to arrestins. *Journal of Neurochemistry*, *90*(3), 576–584.

Oertel, V., Rotarska-Jagiela, A., van de Ven, V. G., Haenschel, C., Maurer, K., & Linden, D. E. (2007). Visual hallucinations in schizophrenia investigated with functional magnetic resonance imaging. *Psychiatry Research*, *156*(3), 269–273.

Silbersweig, D. A., Stern, E., Frith, C., Cahill, C., Holmes, A., Grootoonk, S., et al. (1995). A functional neuroanatomy of hallucinations in schizophrenia. *Nature*, *378*(6553), 176–179.

Sims, A. (2002). *Symptoms in the mind: An introduction to descriptive psychopathology* (3rd ed.). London: Saunders.

Spinnler, H., & Tognoni, G. (1987). Standardizzazione e taratura italiana di test neuropsicologici. *Italian Journal of Neurological Sciences*, *6*(Suppl. 8), 1–120.

Stefanovic, B., Warnking, J. M., & Pike, G. B. (2004). Hemodynamic and metabolic responses to neuronal inhibition. *Neuroimage*, *22*(2), 771–778.

Summerfield, C., Egner, T., Mangels, J., & Hirsch, J. (2006). Mistaking a house for a face: Neural correlates of misperception in healthy humans. *Cerebral Cortex*, *16*(4), 500–508.

Vollenweider, F. X., Leenders, K. L., Scharfetter, C., Maguire, P., Stadelmann, O., & Angst, J. (1997). Positron emission tomography and fluorodeoxyglucose studies of metabolic hyperfrontality and psychopathology in the psilocybin model of psychosis. *Neuropsychopharmacology*, *16*(5), 357–372.

Warrington, E. K., & James, M. (1991). *The Visual Object and Space Perception battery*. Bury St Edmunds, UK: Thames Valley Test Company.

Warrington, E. K. (1984). *Recognition Memory Test*. Windsor, UK: NFER-Nelson.

Wechsler, D. (1997). *Wechsler Adult Intelligence Scale-Third Edition*. San Antonio, TX: The Psychological Corporation.

Wechsler, D. (1999). *Wechsler Abbreviated Scale of Intelligence – Manual*. San Antonio, TX: Psychological Corp.

Wilson, B., Cockburn, J., & Halligan, P. W. (1987). *Behavioural Inattention Test*. Titchfield, UK: Thames Valley Test Company.